

Lymphoma with HIV infection

Themes and variations

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Hypothesis

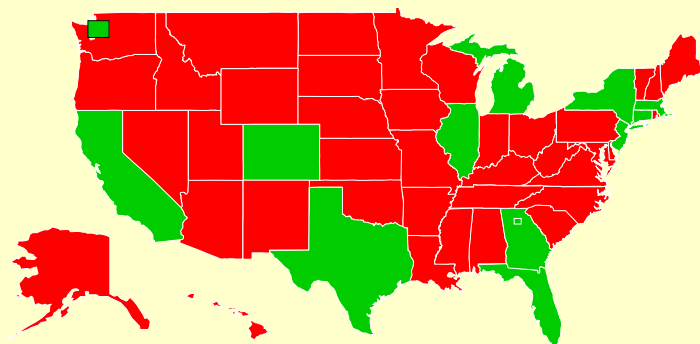
- People with HIV/AIDS (PWA) are at very high risk for lymphomas
 - malignancies associated with viruses.
- Heterogeneity in the risk of lymphomas among PWA may provide insight on the etiology of these malignancies.

Outline

1. Major malignancies among people with HIV/AIDS in the USA, 1980-2002
 - Before, during HAART era
2. Role of immune (CD4 count) deficiency on risk of NHL subtypes
3. Hodgkin lymphoma & EBV
4. Summary

HIV / AIDS CANCER MATCH REGISTRY

Matches cases of HIV/AIDS to reports of cancer in the cancer registries of the same area.



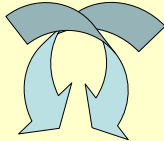
1990-92 100,000 AIDS cases matched
1995-97 300,000 AIDS cases matched
2002-06 500,000 AIDS cases matched

MATCH METHODS

- IRB, LEGAL REVIEWS
- ADVANCE PREPARATION
(PREPARE FILES IN CORRECT COLUMNS)
- ON-SITE: CANCER AND AIDS EACH BRING FULL DATA, NCI BRINGS MATCH PROGRAM
- PROGRAM SORTS DATA USING IDENTIFIERS
(STRIPPED OFF FINAL FILES)
- ANALYSIS DATA FILES RETURNED TO HOSTS
 - EACH REGISTRY GETS ITS OWN FILE
 - IF REGISTRIES AGREE, THESE CAN BE LINKED
- NATIONAL ANALYSES DONE BY NCI STAFF
(OR AS COLLABORATION WITH LOCAL SITE)

LINKAGE PROGRAM

- PROBABILISTIC MATCHING OF IDENTIFIERS
(PERMITS MINOR VARIATION (NUMBER OFF, INVERTED))

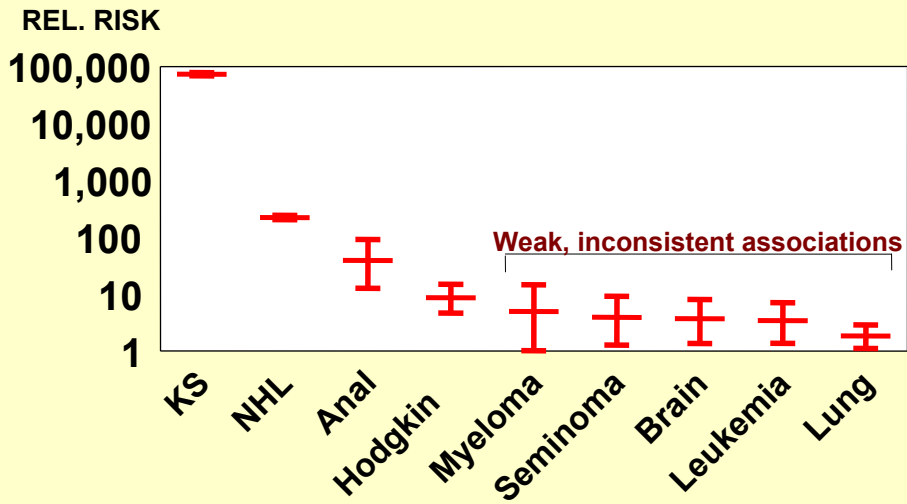
CANCER REG.	EXAMPLE	AIDS REG.
SOC. SECURITY NUM. LAST NAME FIRST NAME DATE OF BIRTH DATE OF DEATH SEX RACE		SOC. SECURITY NUM. LAST NAME FIRST NAME DATE OF BIRTH DATE OF DEATH SEX RACE
LINK SCORE		

SCORE WEIGHED BY FREQUENCY IN DATA BASE

DISPLAY PAIRED SAMPLES BY SCORE STRENGTH, ADDITIONAL INFORMATION (e.g. ADDRESS, MAIDEN NAME)

REVIEWED BY LOCALLY AUTHORIZED PERSONNEL (NOT NCI)
ACCEPTED OR REJECTED (INDIVIDUALLY AND AT A SCORE LEVEL)

HIV / AIDS CANCER MATCH CANCERS INCREASED IN AIDS before 1996



Goedert et al. Lancet 1998; 351:1833; Frisch et al. JAMA 2001; 285:1736

POPULATION IN CURRENT ANALYSES

OVERALL N= 325,516

Males	78.6%
White race	35.7%
30-39 y/o	43.6%
MSM	40.1%

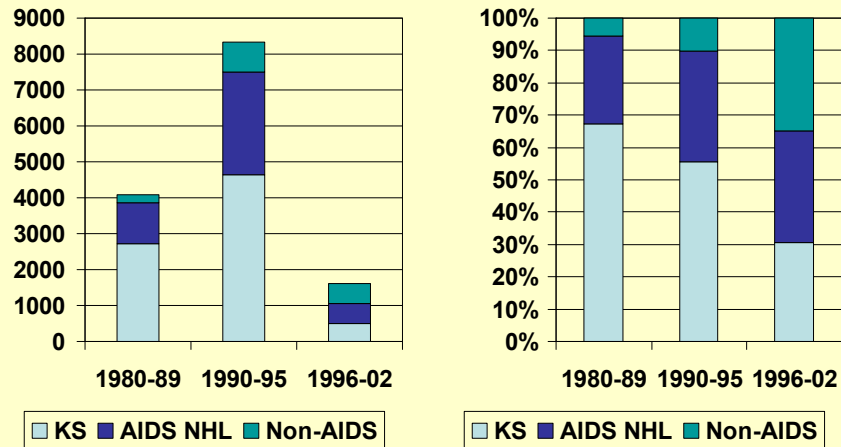
CD4 count at AIDS onset

Known	72.0%
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Distribution:

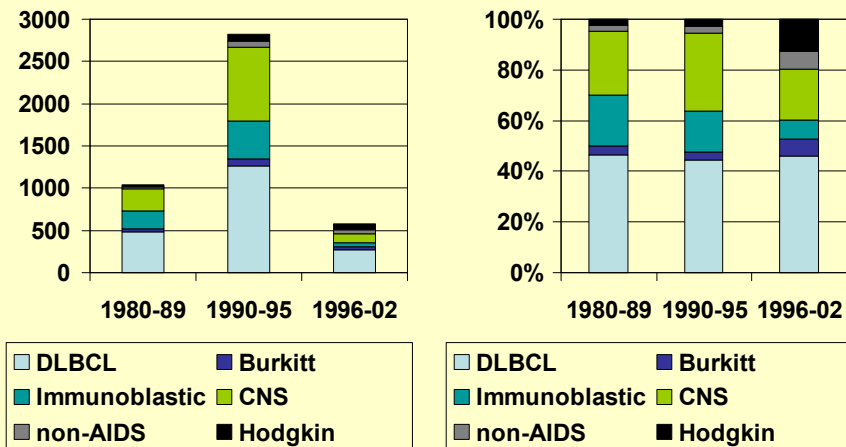
0- 50	47.9%
50-100	16.2%
100-199	37.8%
200-499	14.3%

Major categories of malignancy, by calendar period of AIDS



Engels EA, et al. AIDS 2006;20:1645

Lymphoma categories, by calendar period of AIDS



Engels EA, et al. AIDS 2006;20:1645; Biggar RJ, et al. JNCI 2007;99:962; Cote TR, et al. Internat J Cancer 1997;73:645

**Standardized incidence ratio for major categories of malignancy
among PWA in the USA, by calendar period**

<u>Type of malignancy</u>	<u>SIR*</u>		
	<u>1980-89</u>	<u>1990-95</u>	<u>1996-02</u>
KS	52,900	22,100	3640
Cervix cancer	8	4	5

* SIR, standardized incidence ratio as risk estimate compared to general population.

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Cervix cancer	8	4	5
NHL	80	53	23
-Burkitt	57	53	50
-DLBCL	98	64	30
-Immunoblastic	141	95	60
-CNS	5000	4850	1020

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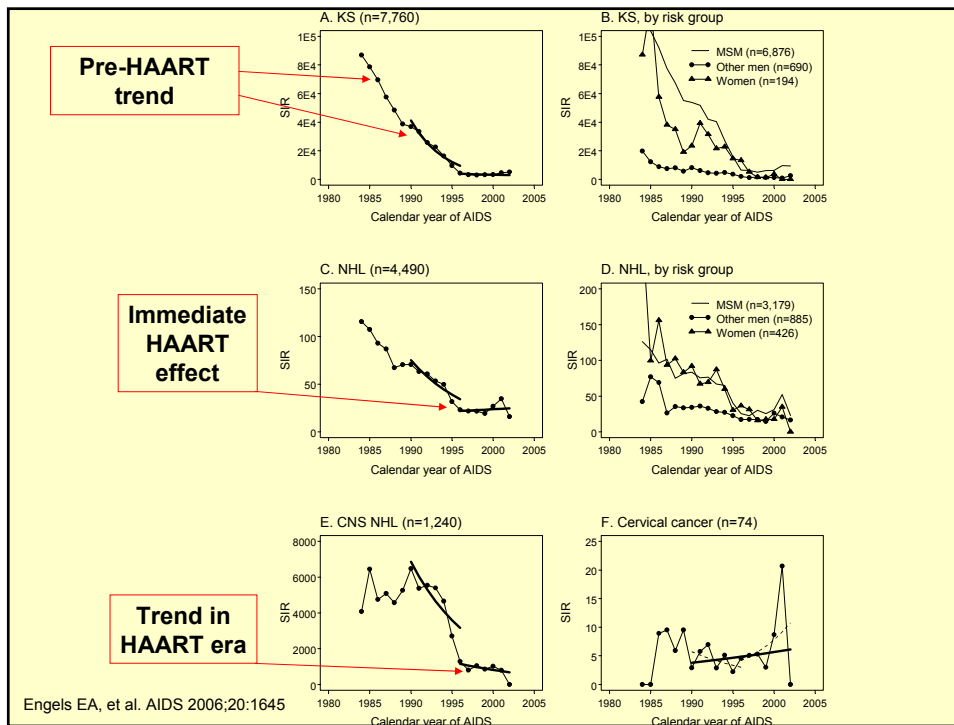
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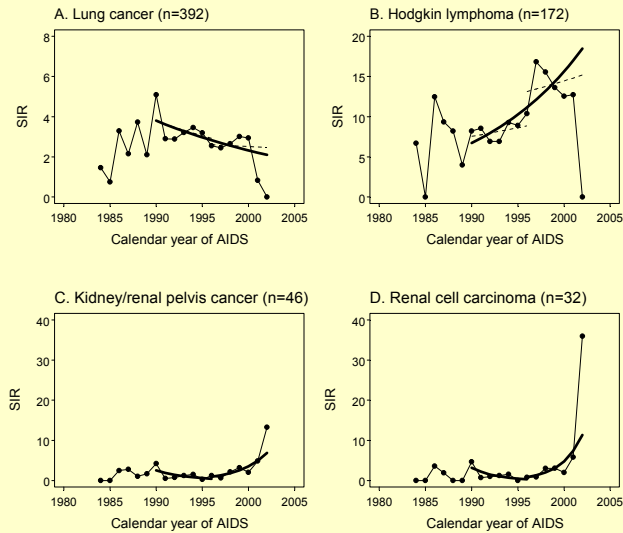
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-CNS	5000	4850	1020
All non-AIDS	2	2	2
-NHL	19	17	11
-Hodgkin	7	8	14
-Anal cancer	18	21	20
-Lung cancer	3	3	3

* SIR, standardized incidence ratio as risk estimate compared to general population.

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Trends in non-AIDS-defining malignancies



Engels EA, et al. AIDS 2006;20:1645

Part 1. CONCLUSIONS

**PERSONS WITH AIDS IN THE USA CONTINUE
TO BE AT HIGHEST ABSOLUTE RISK OF KS,
LYMPHOMAS, AND LUNG CANCER**

**KS AND LYMPHOMA RISKS
HAVE DECREASED IN RECENT
YEARS**

**HODGKIN LYMPHOMA TREND
IS WORRISOME**

Part 2. ROLE OF IMMUNE DEFICIENCY

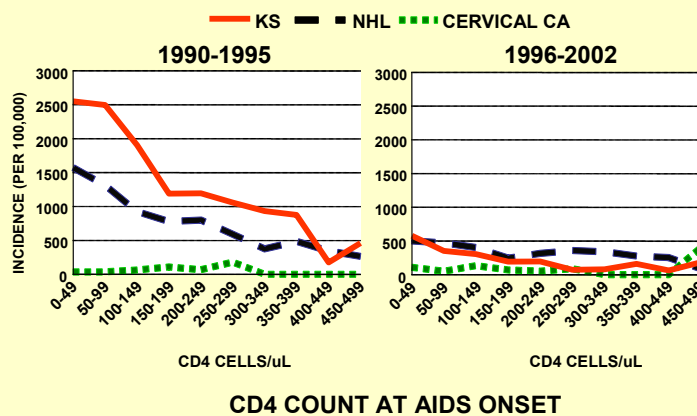
DATA LARGELY LIMITED TO CD4 COUNT AT INITIAL AIDS DEFINING CONDITION (AIDS ONSET)

No CD4 data pre-1990
N=125,669 in 1990-95
N=108,685 in 1996-02

HIV VIRAL LOAD DATA
STILL TOO INCOMPLETE

INCIDENCE OF AIDS-RELATED MALIGNANCIES IN PERSONS WITH AIDS

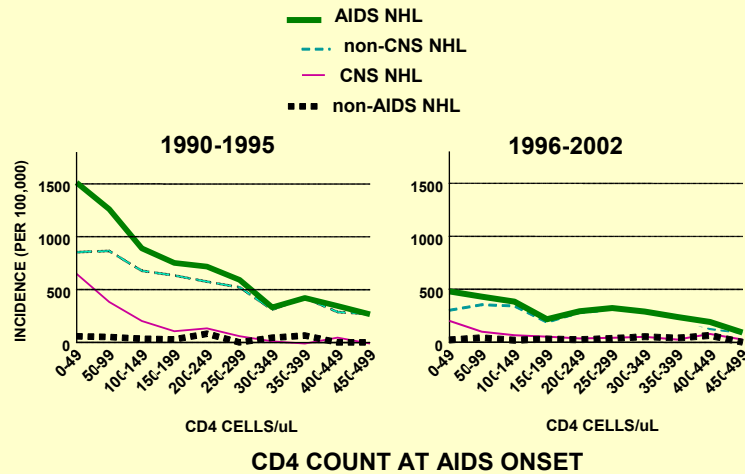
-- BY CALENDAR TIME PERIOD --



<u>Tumor, period</u>	<u>No.</u>	<u>Incidence</u>	<u>Period RR</u>	<u>HR / 50 CD4↓</u>
KS				
- 1990-95	3252	1839		1.28
- 1996-02	501	335	0.22	1.40
NHL, AIDS-defining				
- 1990-95	1862	1023		1.28
- 1996-02	546	362	0.39	1.18

Biggar RJ, et al. JNCI 2007 99:962.

**INCIDENCE OF NON-HODGKIN LYMPHOMA,
AIDS-DEFINING (NON-CNS AND CNS)
AND NON-AIDS-DEFINING TYPES
-- BY CALENDAR TIME PERIOD --**



<u>Tumor, period</u>	<u>No.</u>	<u>Incidence</u>	<u>Period RR</u>	<u>HR / 50 CD4↓</u>
KS				
- 1990-95	3252	1839		1.28
- 1996-02	501	335	0.22	1.40
NHL, AIDS-defining				
- 1990-95	1862	1023		1.28
- 1996-02	546	362	0.39	1.18
CNS				
- 1990-95	570	313		1.76
- 1996-02	117	77	0.27	1.85
Non-CNS DLBC/IB				
- 1990-95	711	391		1.15
- 1996-02	238	158	0.45	1.12
Non-CNS Burkitt				
- 1990-95	73	40		0.93 (ns)
- 1996-02	49	32	0.92 (ns)	0.93 (ns)
NHL, non-AIDS				
- 1990-95	78	43		1.13 (ns)
- 1996-02	43	28	0.65	0.94 (ns)

Biggar RJ, et al. JNCI 2007 99:962.

Part 2. CONCLUSIONS

**AIDS-DEFINING NHL RISK
INCREASED ~25% WITH EACH DECREMENT
OF 50 CD4 CELLS**

**AN AMALGAMATION OF
CNSL: 80% PER DECREMENT
DLBCL: 15% PER DECREMENT
BURKITT: 0% PER DECREMENT**

**CD4 ASSOCIATION HOLDS IN,
AND IS INDEPENDENT OF,
HAART AVAILABILITY**

Part 3. HODGKIN LYMPHOMA (HL)

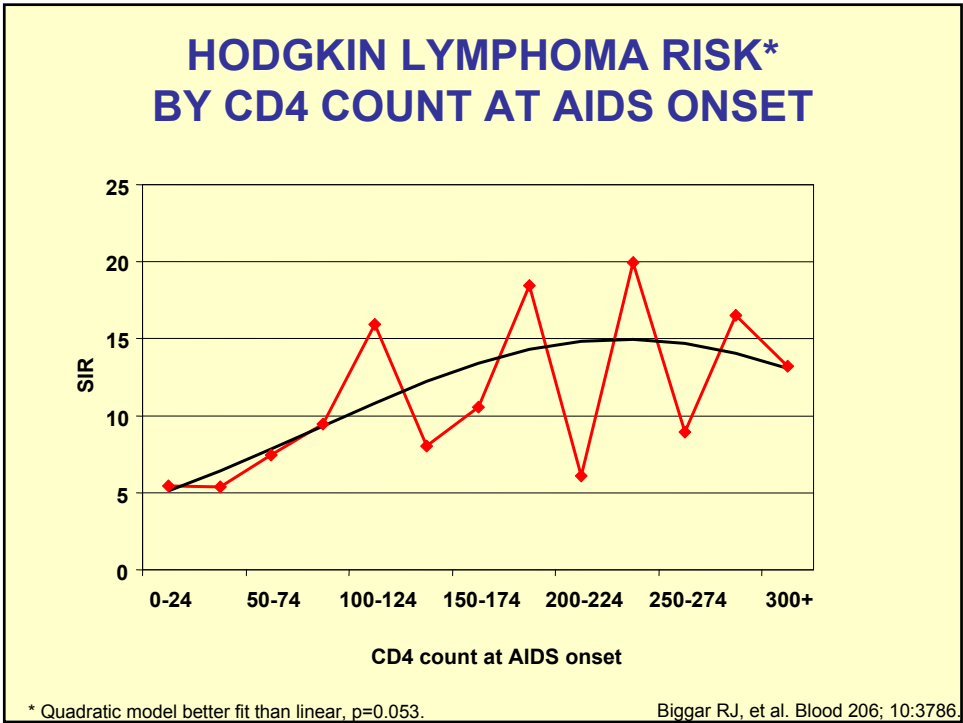
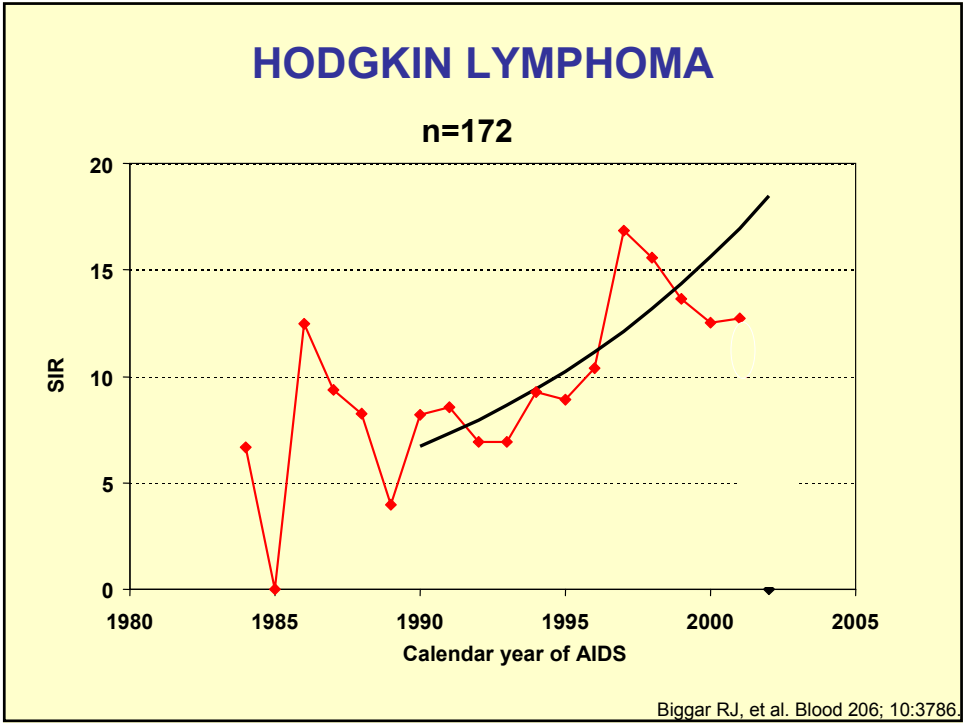
**HL IS NOT “AIDS DEFINING”
BUT IS CONSISTENTLY AND STRONGLY
ASSOCIATED WITH HIV-INDUCED IMMUNE
DEFICIENCY**

**INCREASING HL INCIDENCE IN 1996-2002
SUGGESTS A PARADOXICAL RELATIONSHIP
WITH HAART-INDUCED IMMUNE
RECONSTITUTION**

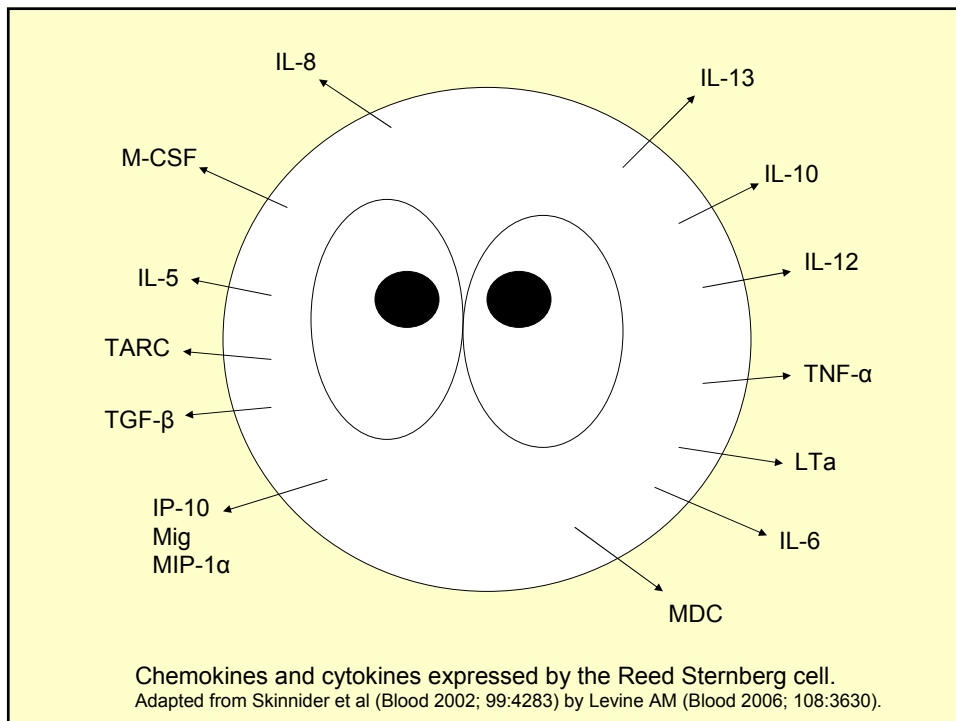
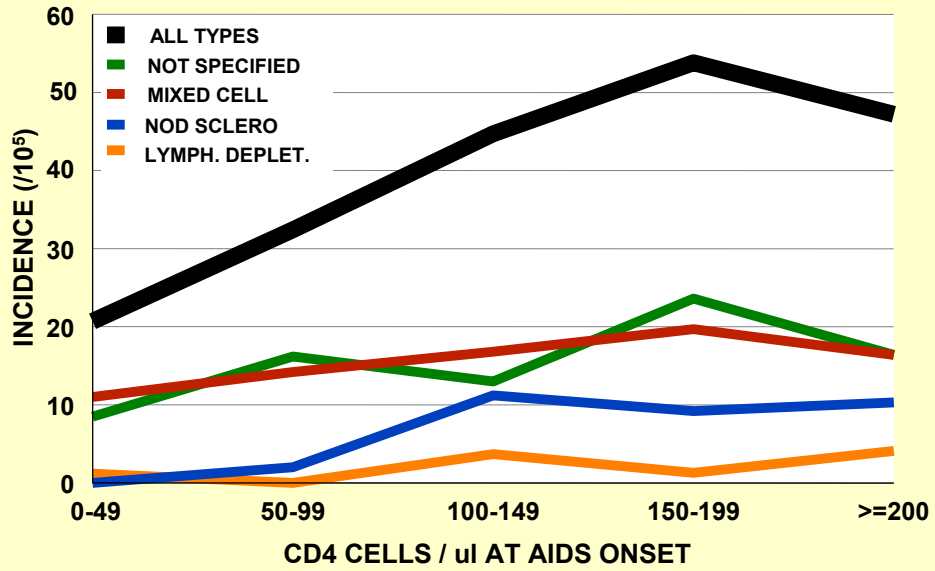
**EBV MAY PLAY AN IMPORTANT ROLE
IN AIDS-ASSOCIATED HL**

<u>Tumor, period</u>	<u>No.</u>	<u>Incidence</u>	<u>Period RR</u>
NHL, AIDS-defining			
- 1990-95	1862	1023	1.0
- 1996-02	546	362	0.39 (0.35-0.44)
Hodgkin lymphoma			
- 1980-89	24	31	1.0
- 1990-95	77	30	0.96 (0.57-1.61)
- 1996-02	72	49	1.60 (0.91-2.82)
			$P_{\text{trend}} = .002$

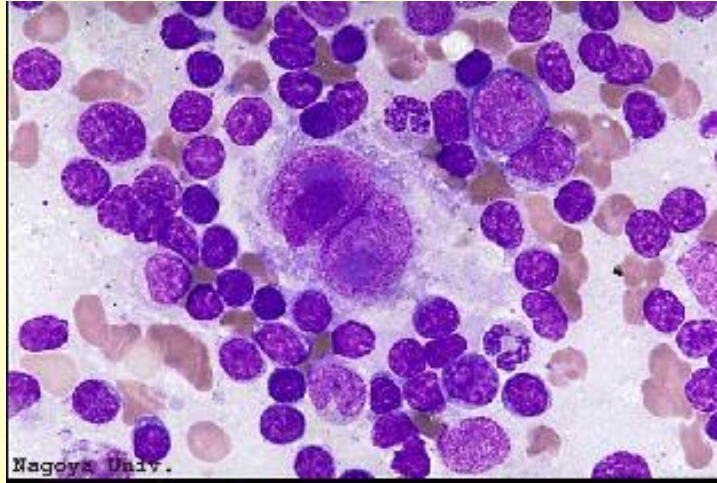
Biggar RJ, et al. JNCI 2007 99:962; Biggar RJ, et al. Blood 2006; 10:3786.



INCIDENCE OF HODGKIN LYMPHOMA 4-27 MONTHS AFTER AIDS ONSET

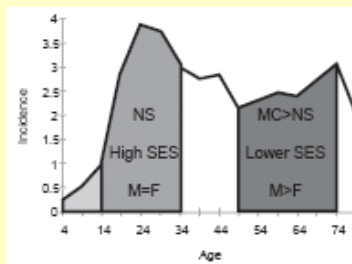


HODGKIN LYMPHOMA REED STERNBERG CELL

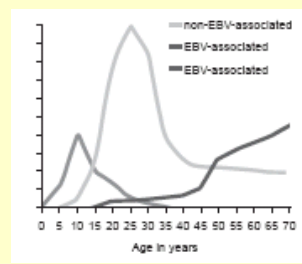


Hodgkin lymphoma models

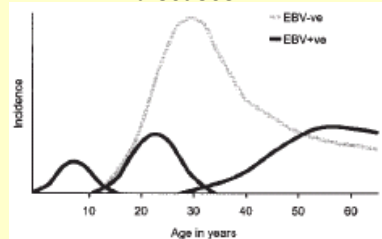
2 diseases



3 diseases



4 diseases



ASSOCIATIONS OF HAART EFFECT, CD4 DEFICIT, & EBV LATENCY IN LYMPHOMAS

<u>Lymphoma</u>	<u>Pre-HAART SIR</u>	<u>HAART effect</u>	<u>RR with 50 CD4↓</u>	<u>EBV+ (latency)</u>
CNS (IBL)	>500	80%↓	1.8	95% (+++)
DLBCL	>300	60%↓	1.2	50%
- centroblastic	-	-	1.1	40% (-)
- immunoblastic	-	-	1.6	90% (+++)
Burkitt (-like)	70	null	null	30% (-)
Other NHL	14	40%↓	null	<10% (-)
Hodgkin	9	60%↑	non-linear	95% (+)

Lost EBV latent antigen responses prior to onset of EBV+ AIDS NHL

Group*	Antigen, cells	Median T-cell responses		
		-6 yrs	-3 yrs	-1 yr
NHL	EBNA1, CD4	349	98	0
HIV+	EBNA1, CD4	341	322	326
	P-value	0.96	0.24	0.053 ←
NHL	BZLF1, CD4	62	90	86
HIV+	BZLF1, CD4	112	112	145
	P-value	0.53	0.43	0.26
NHL	EBNA1, CD8	105	106	0
HIV+	EBNA1, CD8	717	714	421
	P-value	0.33	0.06	0.007 ←
NHL	BZLF1, CD8	1876	542	868
HIV+	BZLF1, CD8	112	275	352
	P-value	0.43	0.54	0.91

* N=9 pre-AIDS EBV+ (EBER) non-CNS NHL.
HIV+ comparison combines pre-other AIDS and HIV+ slow progressors (n=4 each).

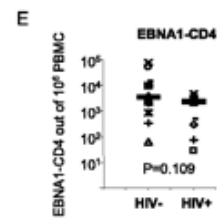
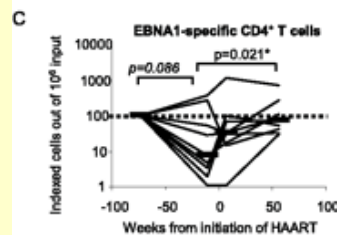
Piriou E, et al. Blood 2005; 106:3166

Effect of HAART on CD4 responses*

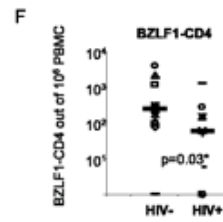
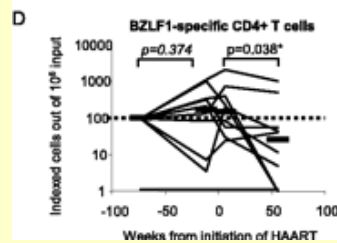
Increase vs latent,
decrease vs lytic

“Normalized” vs latent,
decreased vs lytic

EBV latent
antigen



EBV lytic
antigen



* Similar pattern observed with CD8 responses.

Piriou E, et al. J Immunol 2005; 175:2010

Part 3. CONCLUSIONS

HODGKIN LYMPHOMA RISK IS INCREASING IN THE HAART ERA

SWISS, OTHER COHORTS DEMONSTRATED INCREASED HL RISK
WITH HAART USE

HIGHEST HL RISK AT 100-299 CD4 CELLS/uL

ESPECIALLY MIXED CELLULARITY HL

BELOW 100 CD4 CELLS/uL,
LOW RISK OF NODULAR SCLEROSIS &
LYMPHOCYTE DEPLETED HL

SPECULATION: NHL vs HL OUTCOME
MAY BE AFFECTED BY CELLULAR
RESPONSES, PARTICULARLY DIRECTED
AGAINST EBV LATENT ANTIGENS

SUMMARY

ALL TYPES OF LYMPHOMA, HODGKIN & NON-HODGKIN, ARE INCREASED IN PERSONS WITH AIDS

- CNS and immunoblastic lymphomas – EBV appears central
 - Complete (“Type 3”) EBV latency antigen expression in ~100%
 - Loss of cellular responses to EBNA1 prior to IBL.
 - With HAART, 80% drop in risk, recovery of EBNA1 responses.
- Hodgkin lymphoma – EBV may be important
 - Highest with 100-299 CD4 cells/uL, HAART.
 - H-RS cells have partial (“Type 2”) expression of EBV latency antigens.
- Burkitt lymphoma – EBV may be irrelevant
 - 70% EBV-negative, no latency antigen expression.
 - Risk unrelated to CD4 count, HAART.
 - High c-MYC expression (t8;14) driven by reactive proliferation may be key and may occur early in HIV infection.
- DLBCL and non-AIDS lymphomas – EBV may be irrelevant
 - Most EBV-negative, no EBV latency antigen expression.
 - 40% drop in risk with HAART, modest CD4 count association.

Acknowledgements

Collaborators

Robert Biggar

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Cancer registries

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